

Management of Type-2 Diabetes Mellitus in Adults

Focus on Individualizing Non-Insulin Therapies

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INTRODUCTION

Approximately 25.8 million people in the U.S. (8.3% of the population) are affected by type-2 diabetes mellitus.¹ Even more concerning is that about 79 million adults 20 years of age or older have prediabetes, defined as a glycosylated hemoglobin (HbA_{1c}) level ranging from 5.7% to 6.4%,² and are at risk for the disease.¹

Type-2 diabetes carries significant morbidity and is the leading cause of kidney failure, lower-limb amputations, and new cases of adult blindness. Moreover, it is the seventh leading cause of death in the U.S., primarily as a result of cardiovascular morbidity.³ In terms of financial burden, total direct and indirect costs of the disease are projected to reach \$336 billion annually.⁴ Despite the significant morbidity and mortality associated with this disease, treatment failure (i.e., not achieving goal HbA_{1c}) is common, with one study reporting a failure rate of 63%.⁵

Several therapeutic classes of non-insulin hypoglycemic agents are commonly used to manage hyperglycemia in type-2 diabetes (Table 1).⁶⁻⁸ Appropriate selection is based primarily on patient variables in addition to clinical data. Interestingly, data published in 2010 suggest that regardless of the agent added to metformin (Glucophage, Bristol-Myers Squibb) therapy, additional HbA_{1c} reductions are similar (approximately 0.5%).⁹ These data strengthen the notion that treatment should be individualized, with an emphasis placed on minimizing toxicity while enhancing efficacy.

This article reviews current treatment recommendations for managing hyperglycemia; summarizes the importance of non-glucose goals in diabetes; and provides an overview of non-insulin hypoglycemic agents, including caveats surrounding their use.

TREATMENT GOALS

Non-Glucose Goals

Although tight glucose control is essential for improving outcomes in type-2 diabetes mellitus, research data highlight the importance of non-glucose goals.¹⁰⁻¹³ Patients with longstanding type-2 diabetes may already have complications; therefore, tight blood glucose management in this population might not provide the same degree of benefits compared with newly diagnosed type-2 diabetes and may be detrimental in patients at risk for hypoglycemia.^{10-12,14,15} Targeting non-glucose goals is especially important in this population in order to improve patient outcomes.

The American Diabetes Association (ADA) recommends that patients achieve a low-density lipoprotein-cholesterol (LDL-C) goal of less than 100 mg/dL (below 70 mg/dL in high-risk patients) and a blood pressure (BP) goal of less than 130/80 mm Hg.² Few patients in the U.S. reach the aforementioned goals (BP, 45.5%; LDL-C, 45.6%; aggregate of HbA_{1c}, BP, and

LDL-C, 12.2%).¹⁶

Achievement of non-glucose goals improves outcomes. Controlling hypertension in patients with type-2 diabetes can reduce the progression of cardiovascular disease (CVD) and the risk of microvascular complications (i.e., retinopathy, nephropathy, and neuropathy).¹⁷ Similarly, dyslipidemia confers a greater risk of CVD and is highly prevalent in patients with type-2 diabetes. It is well established that controlling dyslipidemia reduces the risk of CVD-related complications.¹⁷ Clinicians should emphasize not only an attainment of glucose goals but also non-glucose goals in order to optimize outcomes.

Glucose Goals

Both the ADA/European Association for the Study of Diabetes (EASD) and the American College of Endocrinology (ACE) and American Association of Clinical Endocrinologists (AACE) provide guidance in terms of treatment goals and treatment selection. ACE/AACE guidelines are more stringent, suggesting that HbA_{1c} levels be less than 6.5%, whereas the ADA/EASD guidelines recommend a goal of below 7.0%. Suboptimal control of HbA_{1c} is associated with poor outcomes in type-2 diabetes.^{2,6} For every 1% reduction in HbA_{1c}, the risk of microvascular complications is reduced by 33% to 37%.^{13,18}

Recent data have underscored the importance of individualizing HbA_{1c} goals. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial found higher rates of CVD and all-cause mortality with intensive blood glucose lowering (mean HbA_{1c}, 6.4%) compared with standard treatment (mean HbA_{1c}, 7.5%). Furthermore, patients in the intensive blood glucose-lowering arm experienced more hypoglycemic events.¹⁰

Similarly, the Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) trial found no significant differences in major macrovascular events or in all-cause mortality between intensive-treatment patients (mean HbA_{1c} = 6.5%) and standard-treatment groups (mean HbA_{1c} = 7.3%) groups. Rates of hospitalization and severe hypoglycemic events in the intensive glucose-lowering arm were significantly higher.¹² As in the studies described, the Veterans Affairs Diabetes Trial (VADT) revealed that intensive glucose lowering did not reduce CVD or CVD-related deaths, compared with standard glucose lowering, and resulted in a higher incidence of hypoglycemia (in 21%) and weight gain.¹¹ Largely on the basis of these data, the ADA, the American College of Cardiology (ACC), and the American Heart Association (AHA) released a position statement suggesting less stringent goals in patients at risk for hypoglycemia, in those with limited life expectancy, and in those with advanced comorbidities.¹⁹

Early tight blood glucose control may also confer a "legacy

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effect”; therefore, it is prudent that patients with early-stage diabetes achieve optimal glucose control.²⁰

TREATMENT OPTIONS

Nonpharmacological Therapy (Diet and Exercise)

In the Diabetes Prevention Program (DPP) trial, diet and exercise alone decreased the rate of onset of diabetes mellitus by 58% after 3 years.²¹ It is well established that obesity confers an increased risk of developing type-2 diabetes. In one study, both women and men with a body mass index (BMI) greater than 35 kg/m² had a 20 times greater risk of type-2

diabetes compared with individuals with a BMI of 18.5 to 24.9 kg/m².²² The use of metformin, acarbose (Precose, Bayer), or rosiglitazone (Avandia, GlaxoSmithKline) has demonstrated a reduction in conversion of prediabetes to diabetes, but the reductions have not been as dramatic as those observed with diet and exercise.^{8,23}

In addition to reducing conversion to diabetes, diet and exercise reduce fasting plasma glucose (FPG) in obese and non-obese individuals.²⁴ As a result, improved responsiveness to pharmacotherapy and reduced medication requirements may be realized. All patients with type-2 diabetes should be

Table 1 Overview of Currently Available Non-Insulin Hypoglycemic Agents

Drug Class	Expected Decrease in HbA _{1c} With Monotherapy (%)	Contraindications	Disadvantages	Advantages
Biguanides (metformin)	1.0–2.0	Contraindicated with renal dysfunction: • sCr < 1.4; women • sCr < 1.5; women Severe hepatic dysfunction Congestive heart failure requiring pharmacotherapy	GI side effects, megaloblastic anemia (vitamin B ₁₂ deficiency); temporarily discontinue in patients undergoing radiological studies using contrast media	Weight-neutral; few side effects; inexpensive
Sulfonylureas	1.0–2.0		Hypoglycemia, weight gain	Rapidly effective
Thiazolidinediones (e.g., pioglitazone)	0.5–1.4	Class III, IV heart failure	Fluid retention, weight gain, bone fractures, potential increase in MI; use caution if liver impairment	Positive effect on lipid parameters
Alpha-glucosidase inhibitors (e.g., acarbose)	0.5–0.8	Liver cirrhosis, inflammatory bowel disease, colonic ulceration, partial intestinal obstruction	GI side effects, three-times-daily dosing	Minimal risk of hypoglycemia
Meglitinides (e.g., nateglinide)	0.5–1.5	Coadministration of repaglinide (Prandin) with gemfibrozil (Lopid)	Weight gain, three-times-daily dosing	Optimal for postprandial hyperglycemia
Dipeptidyl peptidase (DDP)-4 inhibitors (gliptins)	0.5–0.8		Pancreatitis, lacking long-term safety data	Weight-neutral
Glucagon-like peptide-1 agonists (exenatide, liraglutide)	0.5–1.0	Liraglutide contraindicated in patients with a personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2	Pancreatitis, GI adverse effects, expensive, lacking long-term safety data, must be injected; risk of thyroid C-cell tumors with liraglutide; use caution in gastroparesis	Weight loss
Amylin analogues (Pramlintide)	0.5–1.0	Gastroparesis, hypoglycemia unawareness	Nausea; must be injected	Weight loss
Bile acid sequestrants (colesevelam)	0.5–0.9	Triglycerides > 500 mg/dL	Constipation; drug interactions	Weight-neutral; also reduces LDL-C; not systemically absorbed
Dopamine agonists (bromocriptine)	0.5	Avoid in patients with syncopal migraines; may precipitate hypotension	GI side effects	Weight loss to weight-neutral

GI = gastrointestinal; HbA_{1c} = glycosylated hemoglobin; LDL-C = low-density lipoprotein-cholesterol; MI = myocardial infarction; sCr = serum creatinine.

Data from Rodbard HW, et al. *Endocr Pract* 2009;15:540–559;⁶ and Inzucchi SE, et al. *Diabetes Care* 2012;35:1364–1379.⁸

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encouraged to incorporate diet and exercise into their disease-management plan.

Pharmacotherapy

Although the ADA and AACE guidelines provide recommendations for treatment selection, the ADA guidelines are not stratified by HbA_{1c} levels; they are more general. The AACE stratifies its recommendations according to the patient's baseline HbA_{1c} level and recommends combination therapy if HbA_{1c}

exceeds 7.5%. Figures 1 and 2 illustrate the algorithms suggested by the ADA and AACE, respectively.

Biguanides (Metformin)

Metformin (Glucophage) represents the first-line treatment of type-2 diabetes unless the patient has severe renal disease or is unable to tolerate side effects. Metformin exerts its therapeutic effects by decreasing hepatic glucose production and intestinal absorption of glucose, thereby improving insulin sen-

Antihyperglycemic Therapy in Type-2 Diabetes: General Recommendations

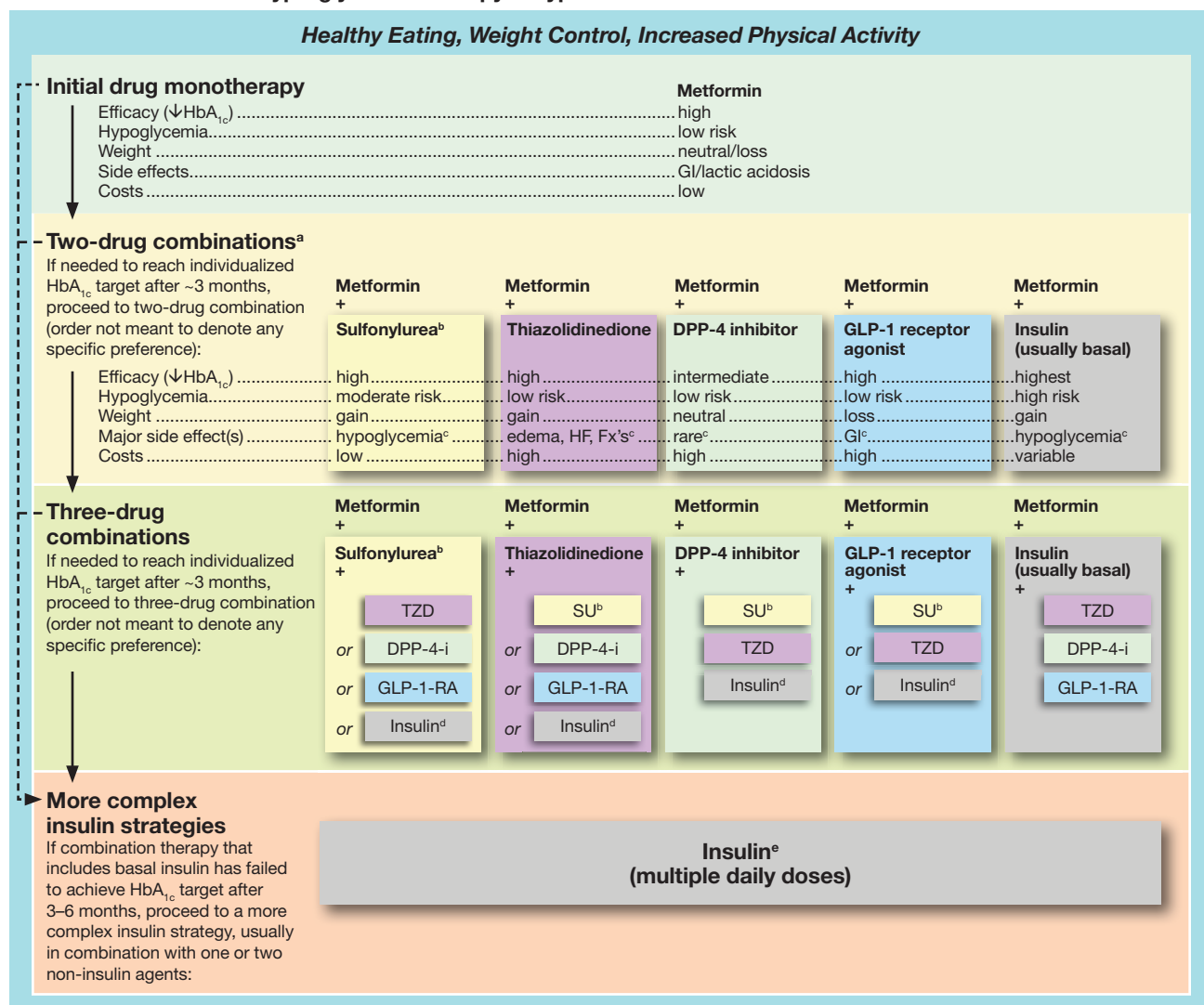


Figure 1 American Diabetes Association algorithm for the treatment of type-2 diabetes mellitus.

^aConsider beginning at this stage in patients with very high glycosylated hemoglobin (HbA_{1c}) (e.g., above 9%).

^bConsider rapid-acting, non-sulfonyleurea secretagogues (meglitinides) in patients with irregular meal schedules or who develop late postprandial hypoglycemia while taking sulfonyleureas.

^cSee Table 1 for additional potential adverse effects and risks.

^dUsually a basal insulin, such as NPH, glargine (Lantus), or detemir (Levemir) in combination with non-insulin agents.

^eCertain non-insulin agents may be continued with insulin; consider beginning at this stage if patient presents with severe hyperglycemia (HbA_{1c} > 10%–12%) with or without catabolic features (weight loss, ketosis).

DPP-4-i = dipeptidyl peptidase-4 inhibitor; Fx's = bone fractures; GI = gastrointestinal; GLP-1-RA = glucagon-like peptide-1 receptor agonist; HF = heart failure; SU = sulfonyleurea; TZD = thiazolidinedione.

(Adapted with permission from Inzucchi SE, et al. *Diabetes Care* 2012;35:1364–1379; © American Diabetes Association.⁸)

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sitivity by increasing peripheral glucose uptake and utilization.

First approved by the FDA in 1994 and marketed in 1995, metformin continues to offer clinicians an excellent therapeutic option with a highly favorable risk-to-benefit ratio. Dosing should be started on the lower end (i.e., 500 mg by mouth twice daily) and gradually increased to minimize gastrointestinal (GI) adverse effects.

In general, doses of less than 1,500 mg daily are unlikely to provide sufficient therapeutic response. In addition to reductions in HbA_{1c} of approximately 1% to 2%, metformin may also result in fewer macrovascular complications. In the original United Kingdom Prospective Diabetes Study (UKPDS) study, overweight patients with newly diagnosed type-2 diabetes who received metformin experienced a 39% ($P = 0.010$) risk reduction for myocardial infarction (MI) and a 36% ($P = 0.011$) reduction

for total mortality after a median follow-up of 10 years. The reduction was not seen in patients who had been randomly assigned to receive sulfonylureas or insulin.²⁵

Metformin therapy is associated with weight loss (or weight-neutrality), causes few adverse drug reactions, rarely results in hypoglycemia when used as monotherapy, and is inexpensive. Decreases in LDL-C and triglyceride levels have also been reported with metformin.²⁶

These data suggest that metformin may lower cancer risk owing to its ability to lower circulating glucose and insulin levels in patients with insulin resistance and hyperinsulinemia.²⁷ Caution is needed in patients with renal dysfunction, a common complication in type-2 diabetes, affecting approximately 40% of patients, because biguanides increase the risk of lactic acidosis.²⁸ Much of the concern with lactic acidosis is based

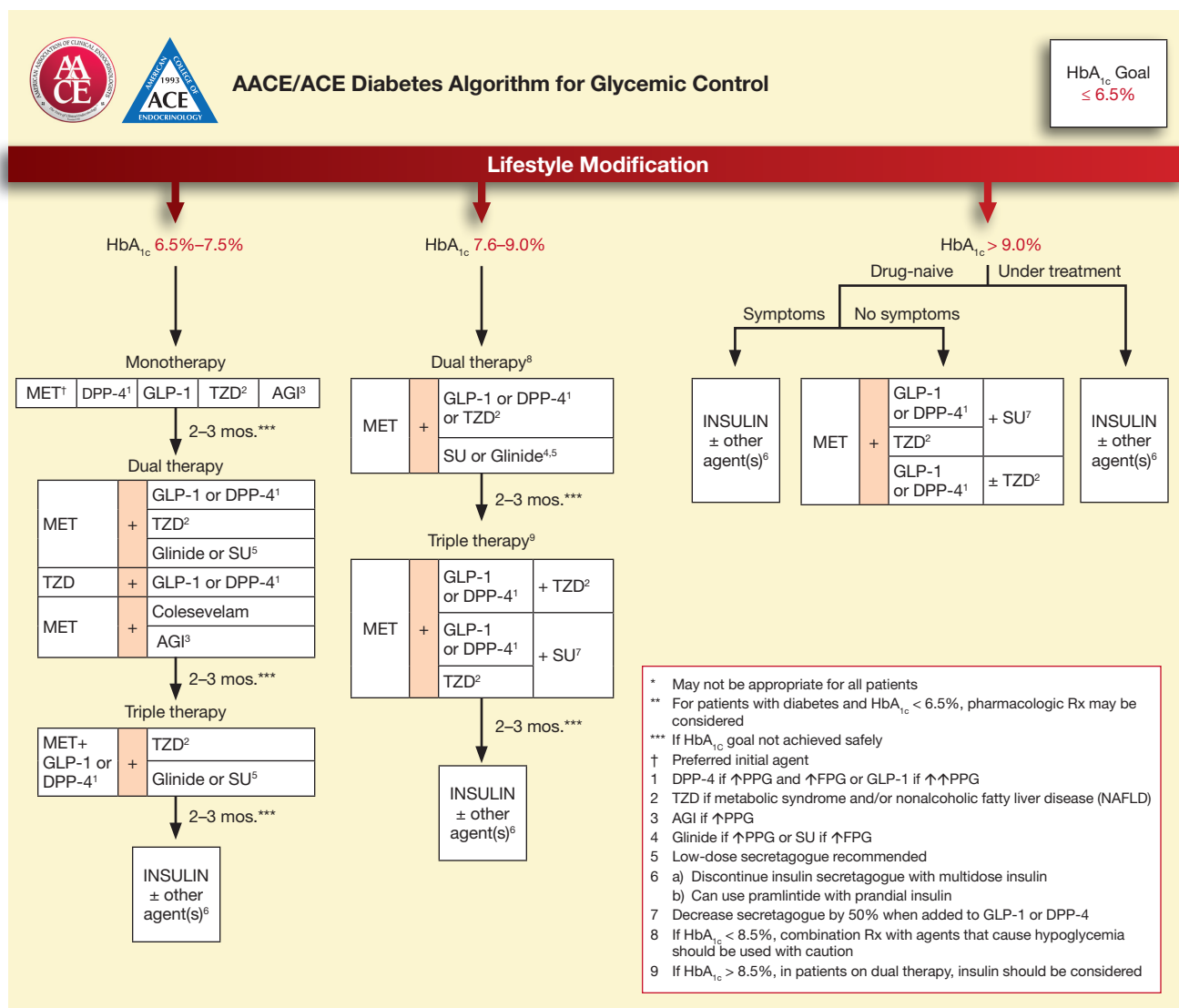


Figure 2 American Association of Clinical Endocrinology algorithm for the treatment of type-2 diabetes. ACE = American College of Endocrinology; AGI = alpha-glucosidase inhibitors; DPP-4 = dipeptidyl peptidase-4; FPG = fasting plasma glucose; GLP-1 = glucagon-like peptide-1; HbA_{1c} = glycosylated hemoglobin; MET = metformin; PPG = postprandial glucose; Rx = prescription; SFU = sulfonylurea; TZD = thiazolidinedione. (Reprinted with permission of the Rodbard HW, et al. © American Association of Clinical Endocrinologists, December 2009 update.⁶)

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on an earlier-generation biguanide, phenformin (formerly DBI, Ciba-Geigy). Compared with metformin, phenformin has a 10 to 20 times increased risk of lactic acidosis. The estimated prevalence of lactic acidosis secondary to metformin is three cases per 100,000 patient-years.^{29,30}

The product labeling suggests that metformin is contraindicated in patients with renal impairment or a serum creatinine (sCr) of 1.4 mg/dL or higher for females and 1.5 mg/dL or higher for males. This complication is rare, and the use of metformin in patients with mild-to-moderate renal disease may be appropriate at reduced doses with careful monitoring.³⁰

It has been suggested that metformin may be safely continued at a reduced dose (in patients stabilized with this drug) if the creatinine clearance (CrCl) is 30 mL/minute or higher, but metformin should not be initiated in patients with a CrCl below 45 mL/minute.³⁰ Other potential side effects associated with metformin include macrocytic anemia secondary to vitamin B₁₂ deficiency, metallic taste, and GI symptoms. Administration with food and a slow escalation of the dosage may ameliorate GI side effects.

Metformin should be avoided in patients experiencing shock, heart failure for which pharmacotherapy is required, severe liver disease, and severe hypoxemia or tissue hypoperfusion.³¹

The most recent edition of the American College of Radiology (ACR) *Manual on Contrast Media* (2010) recommends that clinicians discontinue metformin before administering intravenous (IV) contrast media only in patients at high risk for the development of lactic acidosis.³² The guideline stratifies patients as follows:

- Category I, normal renal function and no comorbidities for lactic acidosis
- Category II, normal renal function and multiple comorbidities for lactic acidosis
- Category III, renal dysfunction

The ACR defines comorbidities for lactic acidosis with metformin use as conditions of decreased metabolism of lactate (liver dysfunction and alcohol abuse) or increased anaerobic metabolism (cardiac failure, myocardial or peripheral muscle ischemia, sepsis, or severe infection).

Patients in category I do not need to discontinue metformin prior to administration of IV contrast media, nor is it necessary to monitor serum creatinine levels following IV contrast media. Patients may resume metformin after 48 hours.

Patients in categories II and III, however, should discontinue metformin, undergo renal function assessment, and resume metformin when appropriate (at least 48 hours after administration of IV contrast media). Nonetheless, many organizations recommend discontinuing metformin for all patients before they receive IV contrast media, monitoring serum creatinine, and restarting metformin after 48 hours if appropriate.

Sulfonylureas (Glimepiride, Glipizide, Glyburide)

First-generation and second-generation sulfonylureas bind to the sulfonylurea receptor on the pancreatic beta-cell surface and ultimately lead to an increase in insulin secretion. Sulfonylureas cause a closure of potassium channels and depolarization of the cell membrane. Opened calcium channels lead to an influx of calcium and an increase in insulin secretion from the pancreas.²⁶

Lower-potency, first-generation sulfonylureas include acetohexamide (Dymelor, Eli Lilly), chlorpropamide (e.g., Diabinese, Pfizer), tolazamide (Tolinase, Pfizer), and tolbutamide (various). Second-generation drugs, including glimepiride (Amaryl, Sanofi), glipizide (Glucotrol, Pfizer), and glyburide (e.g., DiaBeta, Sanofi; Micronase, Pfizer), penetrate cell membranes more easily than first-generation sulfonylureas.

Common adverse events associated with sulfonylureas include weight gain, hypoglycemia, and water retention.²⁶ First-generation sulfonylureas tend to produce an increase in adverse events, ionically bind to plasma proteins, and lead to more drug-drug interactions.

Sulfonylureas increase fasting and late postprandial insulin, leading to decreased blood glucose and HbA_{1c} values. These agents are metabolized in the liver. For renally compromised patients, dosage adjustments must be made with sulfonylureas that have active metabolites or that are excreted renally.

The half-life of these agents corresponds to the risk for hypoglycemia. Patients who are at higher risk for drug accumulation include the elderly, those with renal insufficiency, and those with advanced liver disease. These patients may benefit from starting with a low-dose sulfonylurea that has a shorter half-life. The lowest effective dose of sulfonylurea should be used, and clinicians should be aware that most hypoglycemic effects are seen at half the maximum recommended dose of each respective sulfonylurea.³¹ Glipizide and glimepiride are associated with lower rates of hypoglycemia compared with other sulfonylureas and may be preferred for patients with renal disease and for the elderly.³¹

The recently updated Beers Criteria for Potentially Inappropriate Medications in the Elderly (Beers List) expressed some concerns with the use of long-acting sulfonylureas (i.e., chlorpropamide, glyburide) in the elderly.³³ In general, these agents should be avoided. At equipotent doses, sulfonylureas are equally effective at lowering blood glucose levels. The expected average decrease in HbA_{1c} is 1.5% to 2%. Lower pre-treatment FPG readings increase the risk of hypoglycemic events.³⁴

The University Group Diabetes Program (UGDP) trial identified an increase in deaths from cardiac disease in tolbutamide-treated patients compared with the insulin or placebo groups. The proposed mechanism is the blockage of ischemic preconditioning by inhibition of potassium adenosine triphosphate (ATP) channels within myocardial cells (SUR2A) in addition to beta cells (SUR1). Second-generation sulfonylureas may be more selective for beta-cell receptors and therefore do not block ischemic preconditioning. The U.K. Prospective Diabetes Study (UKPDS 33) followed 3,867 patients with newly diagnosed type-2 diabetes for more than 10 years and found no differences in rates of myocardial infarction (MI) or diabetes-related deaths between the sulfonylurea and insulin groups. Patients in the chlorpropamide, glibenclamide (glyburide), and insulin groups had similar rates of sudden death.

The AACE/ACE Consensus Panel on type-2 diabetes mellitus moves sulfonylureas to a lower priority in dual-combination or triple-combination drug selection because of the potential for hypoglycemia, weight gain, and inability to maintain glycemic control after approximately 1 to 2 years in most patients.^{6,35–37} Although patients initially respond well to this drug class, the durability of the response is short-lived.³⁸ Failure of therapy

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should not be attributed solely to patient nonadherence or poor diet but to a blunted responsiveness to sulfonylureas.

Thiazolidinediones (Rosiglitazone and Pioglitazone)

Rosiglitazone (Avandia) and pioglitazone (Actos, Takeda/Eli Lilly) are the two currently approved thiazolidinediones (TZDs) in the treatment of type-2 diabetes. TZDs improve insulin sensitivity via agonism of the peroxisome proliferator-activated receptor- γ (PPAR). PPAR receptors are located in adipose tissue, skeletal muscle, and the liver. Activation of PPAR receptors leads to the transcription of genes that respond to insulin and that are involved in the transport, utilization, and control of the production of glucose as well as regulation of fatty acid metabolism.

TZDs may be taken without regard to meals and are highly bound to albumin. Pioglitazone is metabolized by cytochrome P450 (CYP) 2C8, 3A4, and hydroxylation/oxidation. Rosiglitazone is metabolized by CYP2C8, 2C9, *N*-demethylation, and hydroxylation. No dosage adjustments are required for either drug in patients with renal impairment. TZDs decrease FPG and postprandial glucose levels.

The expected reduction in HbA_{1c} by TZDs at maximal doses is approximately 1.5% over a period of 6 months. The activity of TZDs depends on the amount of endogenous or exogenous insulin in the body. Other benefits of TZDs include favorable effects on serum lipoprotein and durability of response.

TZDs cause weight gain secondary to fluid retention and increased adipose tissue. Because these agents may cause fluid retention and may precipitate heart failure, they are contraindicated in patients with New York Heart Association class III or class IV congestive heart failure.⁶ In 2007, a meta-analysis including 42 trials showed an association between rosiglitazone and an increased risk of MI (odds ratio [OR], 1.43; 95% confidence interval [CI], 1.03–1.98; *P* = 0.03) and a possible increase in the risk of death from cardiovascular causes (OR, 1.64; 95% CI, 0.98–2.74; *P* = 0.06).³⁹

In the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial, rosiglitazone (plus metformin or a sulfonylurea) was compared with metformin plus a sulfonylurea in the combined endpoint of hospitalization or cardiovascular death. This interim analysis showed inconclusive results.⁴⁰ The Cochrane 2007 review did not find evidence that rosiglitazone increased patient mortality, morbidity, or adverse effects.⁴¹

In evaluating the available safety data in 2007, the Endocrinologic and Metabolic Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee recommended labeling changes for rosiglitazone, including information about ischemic cardiovascular risks, in a boxed warning. In 2010, the FDA required that GlaxoSmithKline develop a restricted access program for rosiglitazone under a Risk Evaluation and Mitigation Strategy (REMS).⁴²

In the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive trial), no statistically significant differences were found in the primary composite endpoint (all-cause mortality, nonfatal MI, stroke, acute coronary syndrome, and revascularization or amputation) between pioglitazone and placebo. The pioglitazone group was observed to have a 16% decrease in the main secondary endpoint (composite of all-cause mortality,

nonfatal MI, and stroke) compared with the placebo group.⁴³

Most of the data do not suggest an increased risk of ischemic heart disease in patients receiving pioglitazone; however, additional study is needed to determine its impact on cardiovascular morbidity and mortality.^{44,45}

TZDs have also been associated with an increased risk of bone fractures in men and women.^{46–48} Caution should be used when considering the use of these agents in patients with or at risk for osteoporosis.

Another concern with TZDs, particularly pioglitazone, is a potentially increased risk of bladder cancer. In an analysis of the French National Health Insurance Plan, 1.5 million diabetic patients with diabetes were observed for a median of 4 years. The analysis found a statistically significant 22% increase in the risk of bladder cancer in pioglitazone-treated patients compared with patients exposed to other hypoglycemic agents (hazard ratio [HR] = 1.22; 95% CI, 1.03–1.43). In response to these data, the French and German regulatory bodies suspended pioglitazone.⁴⁹

A 5-year interim analysis of a planned 10-year epidemiological study found no significant increase in the risk for bladder cancer in patients who were ever exposed to pioglitazone compared with patients who had never received pioglitazone (HR = 1.2; 95% CI, 0.9–1.5).⁵⁰ However, a duration of pioglitazone therapy longer than 24 months was associated with a 40% increase in the risk of bladder cancer (HR = 1.4; 95% CI, 1.03–2.0).

In a separate analysis using the same data set, there was insufficient evidence to suggest that pioglitazone is associated with an increased cancer risk, excluding bladder cancer, in diabetic patients 40 years of age or older.⁵¹ In response to the aforementioned data, the FDA issued a warning in June 2011 urging clinicians to avoid using pioglitazone in patients with active bladder cancer and to use caution when initiating therapy in patients with a history of bladder cancer.⁵² Patients should also be counseled to seek medical attention if they experience symptoms consistent with bladder cancer.

Alpha-Glucosidase Inhibitors (Acarbose, Miglitol)

Currently available alpha-glucosidase inhibitors (AGIs) in the U.S. include acarbose (Precose) and miglitol (Glyset, Pfizer). AGIs work by inhibiting enzymes in the small intestine such as sucrase and maltase.²⁶ Thus, there is a delay in breaking down sucrose and complex carbohydrates. AGIs cause a decrease in postprandial blood glucose in type-2 diabetes (40–50 mg/dL) and may also cause a minor decrease in FPG levels (about a 10% reduction). The impact on HbA_{1c} is minimal, from 0.3% to 1%. Patients with elevated postprandial glucose levels may be candidates for therapy with an AGI.

Adverse effects associated with AGIs include abdominal discomfort, diarrhea, and increased intestinal gas. AGIs should be started at a low dose with one meal daily with the first bite of the meal, and the dose should be slowly titrated upward to three times daily over several months to minimize gastrointestinal (GI) side effects.

Although acarbose is not absorbed from the GI tract, its metabolites are absorbed and excreted in bile. Miglitol is absorbed from the GI tract and excreted via the kidneys. AGIs are most effective in diets consisting of large amounts of carbohydrates. When these medications are used alone, the risk of hypo-

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glycemia is minimal; however, when they are used in combination with insulin secretagogues or insulin, the risk may increase.

The AACE/ACE Consensus Statement on type-2 diabetes mellitus lists AGIs as a monotherapy option for patients with an HbA_{1c} value between 6.5% and 7.5% if postprandial glucose is elevated when metformin is contraindicated. AGIs may also be combined with metformin as a safe dual-therapy option, carrying a minimal risk of hypoglycemia, when the HbA_{1c} value is 6.5% to 7.5%.

AGIs are contraindicated in patients with inflammatory bowel disease or chronic intestinal diseases resulting in impaired digestion or absorption or conditions that might be adversely affected by increased intestinal gas. They are also not recommended if the sCr is greater than 2 mg/dL, because studies have not been conducted in this patient population.⁶

Meglitinides (Nateglinide, Repaglinide)

Nateglinide (Starlix, Novartis) and repaglinide (Prandin, Novo Nordisk) are short-acting insulin secretagogues that stimulate insulin secretion from pancreatic beta cells. With both drugs, glucose is required to stimulate insulin secretion. Both medications are absorbed quickly, have short half-lives, and are highly protein-bound.

Nateglinide is metabolized primarily by CYP2C9 and CYP3A4. It undergoes renal elimination, with no renal dosage adjustments needed. Repaglinide is metabolized via oxidative metabolism and glucuronidation, with no dosage adjustments needed in patients with renal insufficiency; however, prolonged exposure to the medication may occur with hepatic impairment. Nateglinide and repaglinide are taken before each meal.

In a 1-year multicenter randomized, double-blind comparison of repaglinide and glyburide, glyburide was found to reduce HbA_{1c} by 2.4% compared with 1% for repaglinide ($P < 0.05$).⁵³ HbA_{1c} was decreased by 0.5% from baseline with nateglinide and by 0.8% with metformin ($P \leq 0.0001$).⁵⁴

The major adverse effect of this class of medications is hypoglycemia. Weight gain has been noted to a greater degree with repaglinide than with nateglinide. Monotherapy with meglitinides is associated with a reduction in HbA_{1c} of approximately 0.5% to 1.5%. Repaglinide is more effective than nateglinide in terms of HbA_{1c} reduction.²³

Incretins (Exenatide, Liraglutide)

Incretins are peptide hormones that are secreted in response to ingestion of glucose. The major incretins that affect serum glucose levels are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP). The primary mechanisms through which incretins exert their effects include glucose-dependent stimulation of insulin synthesis and secretion (GLP-1 and GIP), suppression of glucagon release (GLP-1), and delaying gastric emptying and increasing satiety (GLP-1).⁵⁵

GIP is normally secreted in patients with type-2 diabetes; however, the beta cells are less sensitive to its effects. The effects of GLP-1 are not blunted in these patients; therefore, GLP-1 represents a viable therapeutic target. After GLP-1 is secreted from the L cells of the intestinal mucosa, approximately 50% of GLP-1 is degraded by dipeptidyl peptidase-4 (DPP-4) within minutes.⁵⁶ Less than 15% of endogenously secreted GLP-1 actually reaches the pancreas.⁵⁷ The half-life

of endogenous GLP-1 is 1 to 2 minutes.⁵⁷ The understanding of this physiology supports the use of both endogenous GLP-1 agonists and DPP-4 inhibitors.

Two short-acting injectable GLP-1 agonists—exenatide (Byetta, Amylin) and liraglutide (Victoza, Novo Nordisk)—and a once-weekly, extended-release formulation of an exenatide suspension (Bydureon, Amylin/Alkermes) are approved by the FDA. The half-lives of these GLP-1 agonists are significantly longer than that of endogenous GLP-1 (1 to 2 minutes)—2.4 hours for exenatide and 13 hours for liraglutide.

Exenatide and liraglutide are resistant to enzymatic degradation by DPP-4.⁵⁷ Both short-acting agents decrease HbA_{1c} by about 0.5% to 1.0% and promote a weight loss of approximately 2 to 3 kg after 6 months of treatment. The mechanism of weight loss is related to increased satiety and the delay in gastric emptying resulting from the exogenous administration of GLP-1; therefore, GLP-1 therapy might not be appropriate in patients with severe GI disease (i.e., gastroparesis).

The most common side effects of these agents include GI symptoms, with 50% of patients experiencing nausea upon therapy initiation. GLP-1 agonists have a low risk of hypoglycemia and may be an appropriate option in obese patients. An increase in the risk of pancreatitis has been noted with GLP-1 agonists; however, data are conflicting.^{58–61} GLP-1 agonists may also increase the risk of acute renal failure; therefore, they should be avoided in patients with severe renal disease.^{6,23}

The long-acting, once-weekly formulation of exenatide (Bydureon) has the advantage of providing a long interval with increased efficacy. It has also helped patients achieve HbA_{1c} reductions of 1% to 1.9% and weight reductions of up to 4 kg.^{62,63}

DPP-4 Inhibitors (The Gliptins)

Several DPP-4 inhibitors have been approved, including sitagliptin (Januvia, Merck), saxagliptin (Onglyza, Bristol-Myers Squibb/AstraZeneca), and linagliptin (Tradjenta, Boehringer Ingelheim). The efficacies of these agents have been established in several randomized controlled trials. These agents are well tolerated, carry a low risk of hypoglycemia, and are weight-neutral.⁶⁴

Several published studies propose that DPP-4 inhibitors may have a protective cardiovascular effect.⁶⁵ Suggested mechanisms include improved heart function and coronary perfusion, reduced blood pressure, and favorable effects on the lipid profile.^{65,66} Further data are needed to determine whether DPP-4 inhibition improves cardiovascular outcomes in type-2 diabetes. Expected reductions in HbA_{1c} values with the use of DPP-4 inhibitors range from 0.5 to 0.8%.⁸

Dosage adjustments are required for both sitagliptin and saxagliptin in patients with renal disease, whereas no dosage alterations are necessary for linagliptin, which might be preferred in patients with significant renal disease.⁶⁷ DPP-4 inhibitor therapy should be discontinued in patients presenting with acute pancreatitis, and patients should not be rechallenged.

Although clinical trials of DPP-4 inhibitors suggested an increased risk of upper respiratory tract infections, urinary tract infections, and nasopharyngitis, a meta-analysis published in 2012 did not find any increased risk compared with other treatments.⁶⁶ DPP-4 inhibitors provide a safe and effective option for patients with type-2 diabetes and may be preferred in elderly

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individuals, given their weight-neutrality, low propensity for hypoglycemia, and safety in renal impairment.⁶⁵

Hormone Analogues (Pramlintide)

Patients with type-2 diabetes have diminished levels of amylin, a hormone secreted by the pancreatic beta cells. Amylin suppresses glucagon secretion, slows gastric emptying, and suppresses appetite.⁶⁸ Pramlintide (Symlin, Amylin Pharmaceuticals) is a synthetic form of amylin approved as an adjunct to insulin in both type-1 and type-2 diabetes. Pramlintide acts on postprandial glucose, and multiple daily pre-meal injections are required. The most common side effects are GI upset, nausea, and hypoglycemia. Insulin requirements may be decreased upon initiating therapy, especially in patients with type-1 diabetes.

The starting dose of pramlintide in type-2 diabetes is 60 mcg, administered subcutaneously before meals. HbA_{1c} reductions of approximately 0.5% and a weight loss of 1 to 1.5 kg over a period of 6 months may be achieved with pramlintide.⁶⁹

Bile Acid Sequestrants (Colesevelam)

In addition to its role in managing hyperlipidemia, colesevelam (Welchol, Sankyo Pharma) is approved by the FDA as an adjunct to diet and exercise to improve glycemic control in adults with type-2 diabetes.⁷⁰ Colesevelam is a bile acid sequestrant engineered to have higher specificity and binding capacity with bile acids compared with older-generation agents. Several plausible mechanisms have been proposed for the glucose-lowering effects in type-2 diabetes, including effects on insulin sensitivity and secretion, changes in bile acid composition, and incretin effects.⁷¹ Bile acid sequestrants may also influence serum glucose levels via their effects on the farnesoid X receptor (FXR), the liver X receptor, TGR5/GLP-1, and GIP.⁷¹⁻⁷³ Current data suggest that colesevelam may have a role in the management of type-2 diabetes as well as in patients who have not achieved LDL-C goals with statins (HMG-CoA reductase inhibitors) alone. HbA_{1c} reductions of approximately 0.5% are expected as well as reductions in LDL-C levels of 13% to 17%.⁷⁰

Advantages of colesevelam include a lack of systemic absorption, no appreciable impact on organ dysfunction upon administration, and efficacy in both glucose and lipid control. Colesevelam should be avoided in patients with bowel obstruction and hypertriglyceridemia.

Systemic drug interactions are unlikely with colesevelam, because absorption is negligible, but colesevelam has the potential to bind medications in the GI tract. Medications that are known to be bound by colesevelam should be taken at least 4 hours before colesevelam. Overall, colesevelam represents a possible option as an adjunctive therapy for type-2 diabetes that helps patients achieve both LDL-C and HbA_{1c} goals. As such, type-2 diabetic patients with hyperlipidemia who are not at their LDL-C goal may benefit from the addition of colesevelam.

Dopamine Agonists (Bromocriptine)

Bromocriptine mesylate (Parlodel, Novartis) has been used in the U.S. for more than 30 years, but was only recently granted FDA approval for the treatment of type-2 diabetes. Although the exact mechanism of action has not been defined, it has been postulated that bromocriptine resets the central nervous system regulatory pathways responsible for metabolic

control.⁷⁴ Agents that block dopamine activity are associated with impaired metabolism, weight gain, insulin resistance, and dyslipidemia.⁷⁴ Based on these data, it is plausible that restoring dopamine balance with bromocriptine might re-establish centrally mediated metabolic pathways.

The starting dose of bromocriptine is 0.8 mg once daily, with a maximum recommended dose of 4.8 mg once daily. In published phase 3 clinical trials, a dosage of 2.5 to 4.8 mg daily helped patients achieve HbA_{1c} reductions of approximately 0.6 to 0.7%.⁷⁵

Another positive attribute of bromocriptine is its favorable effects on weight. In clinical trials, it had either no effect or small reductions in weight. Bromocriptine also results in reduced plasma triglyceride and free fatty acid levels in type-2 diabetes.⁷⁵

The most common adverse effects in clinical trials were gastrointestinal, including nausea in 26% to 33% of patients and vomiting in 5% to 8% of patients. The safety profile of bromocriptine was highlighted in an industry-sponsored study with 1 year of follow-up (n = 3,070). Adverse events, including hypoglycemia, occurred more often with bromocriptine than with placebo.

Some concerns with bromocriptine include a risk of orthostatic hypotension and syncope. This drug is contraindicated for patients with syncopal migraines. Bromocriptine is not recommended for patients with severe psychotic disorders. According to some clinical data, bromocriptine may have a niche in obese patients with elevated triglyceride levels. Ultimately, additional long-term studies are needed to establish the durability of bromocriptine and to define its role in type-2 diabetes.

DISCUSSION

Although several therapeutic drug classes are available to aid clinicians in achieving glucose goals in type-2 diabetes, patients often have comorbidities that reduce the viable treatment options. Sixty percent of patients with diabetes have at least one comorbidity, and approximately 40% have at least three.^{76,77} To add to this complexity, many patients require multiple agents for optimal disease management. After 3 years of treatment in the UKPDS study, only 50% of patients had glucose control with monotherapy, and after 9 years of treatment, only 25% of patients achieved glucose control.⁷⁸

Type-2 diabetes comprises multiple defects; therefore, choosing agents with complementary mechanisms of action is another rational approach to enhancing outcomes. Choosing the appropriate treatment often presents a clinical conundrum because of the plethora of variables to consider.

In addition to choosing an efficacious treatment, patient safety must be considered in order to minimize the risk of hypoglycemia. An evaluation of reports to U.S. poison control centers between 2001 and 2010 identified a 74% increase in oral hypoglycemic exposures.^{79,80} In an evaluation of emergency hospitalizations for adverse drug reactions in adults 65 years of age and older, oral hypoglycemic agents were implicated in 10.7% of cases.⁸¹ With the increasing prevalence of type-2 diabetes, this number is likely to continue to rise.

Some adverse effects may be avoided by careful selection and consideration of patient variables. Careful review of patient parameters can aid in selecting the most appropriate treatment and minimizing unwanted toxicities. The American Geriatric Society guideline for caring for older diabetic patients highlights the importance of recognizing the heterogeneity of this age

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group when delineating and individualizing treatment selection and goals for them.⁸² Tailoring treatment may help achieve desired outcomes in a broad population by minimizing unwanted toxicities and interactions and by improving patient acceptance.

Medication adherence is often suboptimal in patients with type-2 diabetes because of forgetfulness, medication costs, depression, concern about weight gain, and hypoglycemia.⁸³ Patient preferences and input may aid clinicians in choosing regimens that facilitate medication adherence. Clinicians should consider strategies to improve patient tolerability and adherence, such as reducing the pill burden or asking patients about their preferences for treatment.

Overall, when developing a treatment regimen, practitioners should consider the medication efficacy's and the likelihood of achieving therapeutic goals; the safety profile; patient parameters that could affect the drug's safety and efficacy; the patient's preferences; and synergistic mechanisms of action.

CONCLUSION

Successful management of type-2 diabetes mellitus involves targeting both glucose and non-glucose goals in order to achieve the greatest reduction in morbidity and mortality. A variety of pharmacological agents, each with its benefits and risks, are available to manage hyperglycemia in diabetes. Treatment choice and therapeutic targets should be individualized and based on clinical data as well as patient parameters.

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